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The Inherent Stability of Collagen

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Collagen is an important protein, that has an interesting secondary and tertiary structure. Three protein strands wind around each other, conserving the ε_L secondary structure. Here we explore theoretically the experimentally known thermodynamic properties of amino acid triplets on the triple helix structure. Gibbs free energy values are in complete accordance with experiments. Sarcosine (N-methyl glycine) also seems to stabilize the triple helix.

1 Introduction

Collagen is an important extracellular protein, it provides one quarter of the proteins in our body. Tropocollagen is the well-known triple helix formed by three protein chains wound around each other.¹ In each chain, glycine must be in every third place, and these places are displaced with one residue in each chain.¹ Collagen chains contain amino acid residues only in one conformation, which is characterized by the dihedral angles $\phi = -70^\circ$, $\psi = 150^\circ$, and is sometimes called ε_L .¹ Interestingly, the X-ray structure of polyglycine-II has the amino acids in the same conformation. According to our previous results⁷, the most stable conformation for the glycine amino acids – where every amide bond is having two hydrogen bonds with two neighboring amide bonds – is this ε_L . For amino acids having an alkyl side chain, the β -pleated sheet is the most stable conformation.⁷ This is the building block of amyloid, and of other plaques also, that are known to cause conformation diseases and so dementia.³ Furthermore, it has been discovered recently that several proteins are able to form such plaques (e.g. myoglobin), after some environmental treatment.² Therefore plaque formation seems to be the inherent nature of proteins.⁷ As a consequence, to prevent its every protein turn into a β -pleated sheet plaque, nature uses several strategies.⁴ For collagen, this strategy might be the conservation of another secondary structure (the ε_L).

2 Methods

18 (3*6) residue containing collagen and triple stranded β -pleated sheet models were created as described before⁸. For all calculations the Gaussian 03⁶ software was used. The structures were optimized with the “tight” criteria and subsequent frequency calculations were carried out, both at the B3LYP/6-31G(d) level of theory. Frequency calculations allow us to obtain entropy and Gibbs free energy data. The models discussed here contain

- (i) only glycine amino acids (called GGG),
- (ii) glycine and alanine (called AAG),
- (iii) glycine and sarcosine (N-methyl glycine) (called SaSaG),
- (iv) glycine and proline (called PPG),
- (v) glycine and proline and hydroxyproline (called POG).

The reference values of the enthalpy and Gibbs free energy results are the sums of the enthalpies (Gibbs free energies) of the three individual peptide strands, 6 residues long each.

3 Results

Enthalpy and Gibbs free energy values of the triple helical collagen mimicking structure and the triple stranded β -pleated sheet for each amino acid composition can be seen on Table 1.

	ΔH (kcal/mol)		ΔG (kcal/mol)	
	triple helix	β -pleated sheet	triple helix	β -pleated sheet
GGG	-30.9	-68.5	27.2	-16.4
AAG	-29.0	-70.1	19.5	-29.3
SaSaG	-60.7	-44.3	-15.9	-2.9
PPG	-40.6	-9.9	0.3	21.8
POG	-40.6	-15.7	-1.3	13.1

Table 1. Enthalpies and Gibbs free energies of the triple helical and β -pleated sheet models.

For the GGG and AAG models, the sheet is the most stable structure. The Gibbs free energy of the triple helices are much higher than that of the beta sheet and also than that of the individual strands. Regarding the enthalpy values, the triple helices are more stable than the individual strands, however, the β -pleated sheet is much more stable. Experimental results⁵ show that these triplets indeed destabilize the triple helix. For the SaSaG, PPG and POG triplet containing models both the enthalpy and Gibbs free energy results indicate the stability of the triple helix over the β -pleated sheet. However, a very interesting result can be seen: for the PPG and POG models the triple helix, even though it is more stable than the β -pleated sheet, has the same amount of energy as the individual strands. On the contrary, the SaSaG triple helical model is quite stable with respect to the individual strands. Unfortunately there are no experimental results for the SaSaG triplet in a triple helix, however it is shown that PPG and POG stabilizes the collagen.

4 Conclusions

In concordance with experimental results we can say that our calculations have also shown that the GGG and AAG triplets destabilize and the PPG and POG triplets stabilize the

collagen triple helix. For our great surprise sarcosine stabilizes the triple helix in a much greater extent than proline and hydroxyproline. Therefore a possible strategy for collagen to “prevent itself” from plaque formation is to eliminate the two NH amide hydrogen per three amino acids that are not included in internal hydrogen-bond formation. This can be done simply by applying a methyl group instead of the hydrogen (SaSaG). Indeed, here the triple helix is more stable than the β -pleated sheet, in a much larger extent than in the case of PPG and POG. It is very interesting, as the triple helix stabilizing effect of the proline and hydroxyproline is known for a long time. An other interesting point is that these Gibbs free energy results are in complete accordance with experimental stability data, contrary to the simple energy difference results⁸.

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References

1. A. Bhattacharjee and M. Bansal, *Collagen structure: The Madras triple helix and the current scenario*, IUBMB Life **57**, 161, 2005.
2. C. M. Eakin, A. J. Berman and A. D. Miranker, *A native to amyloidogenic transition regulated by a backbone trigger*, Nat. Struct. Mol. Biol. **13**, 202-208, 2006.
3. J. C. C. Chan, N. A. Oyler, W. M. Yau and R. Tycko, *Parallel beta-sheets and polar zippers in amyloid fibrils formed by residues 10-39 of the yeast prion protein Ure2p*, Biochemistry-US **44**, 10669, 2005.
4. C. F. Wright, S. A. Teichmann, J. Clarke and C. M. Dobson, *The importance of sequence diversity in the aggregation and evolution of proteins*, Nature **438**, 878, 2005.
5. V. C. Chan, J. A. M. Ramshaw, A. Kirkpatrick, K. Beck and B. Brodsky, *Positional preferences of ionizable residues in Gly-X-Y triplets of the collagen triple-helix*, J. Biol. Chem. **272**, 31441, 1997.
6. M. J. Frisch et al., Gaussian, Inc.: Wallingford CT, 2004.
7. A. Perczel, P. Hudaky and V. K. Palfi, *Dead-End Street of Protein Folding: Thermodynamic Rationale of Amyloid Fibril Formation*, J. Am. Chem. Soc. **129**, 14959, 2007.
8. V. K. Palfi and A. Perczel, *How Stable is a Collagen Triple Helix? An Ab Initio Study on Various Collagen and β -Sheet Forming Sequences*, J. Comp. Chem. **29**, 1374, 2008.

